Exhibit 2

1. WO2020010643 - METHOD FOR SYNTHESIZING VALSARTAN

PCT Biblio.Data | Full Text | ISR/WOSA/A17(2)(a) | National Phase | Patent Family | Notices | Documents

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发明名称 0001 0002 0003 0004 0005 0006 0007 0008 0009 0010 0011 0012 0013 0014 0015 0016 0017 0018 0019 0020 0021 0022 0023 0024 0025 0026 0027 0028 0029 0030 0031 0032 0033 0034 0035 0036 0037 0038 0039 0040 0041 0042 0043 0044 0045 0046 0047 0048 0049 0050 0051 0052 0053 0054 0055 0056 0057 0058 0059 0060 0061 0062 0063 0064 0065 0066 0067 0068 0069 0070 0071 0072 0073 0074 0075 0076 0077 0078 0079 0080 0081 0082 0083 0084 0085 0086 0087 0088 0089 0090 0091 0092 0093 0094 0095 0096 0097 0098 0099 0100 0101 0102 0103 0104 0105 0106 0107 0108 0109 0110 0111 0112 0113 0114 0115 0116 0117 0118 0119 0120 0121 0122 0123 0124 0125 0126 0127 0128 0129 0130 0131 0132 0133 0134 0135 0136 0137 0138 0139 0140 0141 0142 0143 0144 0145 0146 0147 0148 0149 0150 0151 0152 0153 0154 0155 0156 0157 0158 0159 0160 0161 0162 0163 0164 0165 0166 0167 0168 0169 0170 0171 0172 0173 0174 0175 0176 0177 0178 0179 0180 0181 0182 0183 0184 0185 0186 0187 0188 0189 0190 0191 0192 0193 0194 0195 0196 0197 0198 0199

claims

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

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Invention name: A kind of synthetic method of valsartan

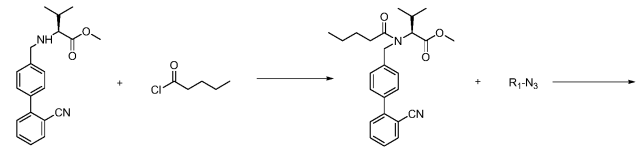
[0001] This application claims the priority of the Chinese patent application filed on July 13, 2018 with the application number of 201810771261.1 and the title of the invention is "a method for synthesizing high-purity valsartan", the entire contents of which are incorporated herein by reference Applying.

technical field

[0002] The invention relates to the technical field of medicines, in particular to a method for synthesizing valsartan.

Background technique

[0003] Valsartan is a widely used antihypertensive drug in clinical practice. It has the advantages of small side effects and good tolerance. It can also be used for the treatment of hypertension in patients with diabetes and kidney disease. The pharmacophore in the valsartan molecule is biphenyl tetrazolium. In the production of commercial products, the most common construction strategy for the tetrazolium ring is to synthesize cyanobiphenyl compound and azide at high temperature. The general commercial production route of such valsartan is expressed as follows:

[0004] 

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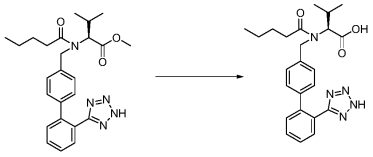

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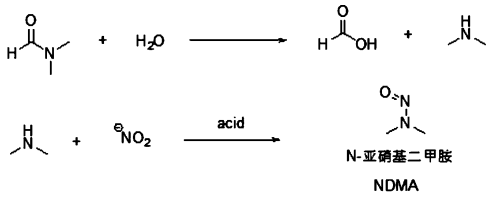
[0005] R_1 represents a group such as Na, K or TMS.

[0006] In the above-mentioned synthetic route of valsartan, the most suitable solvent in the process of tetrazolium cyclization is N,N-dimethylformamide (DMF); this is because DMF has excellent solubility and relatively high When DMF is used as the solvent, the reaction substrate valsartan cyanide has the highest conversion rate, and the palm molecule in the reaction substrate is the most stable in DMF solvent under high temperature conditions, and is not easy to racemize to generate isomer impurities. At the same time, in commercial production, in order to ensure that the valsartan cyanide intermediate is fully converted in the reaction process, the azide reactants such as sodium azide, potassium azide or $TMSN_3$ are used in excess in the reaction; After the reaction is completed, if the azide is not quenched, toxic azide acid will be produced in the subsequent process; at the same time, when the azide-containing material is in contact with the material containing copper or other transition metal materials during the transfer process, it is very difficult. Explosion is prone to occur; therefore, in order to ensure the safety of operation, the residual azide in the process must be quenched by destroying the residual azide with nitrite under acidic conditions.

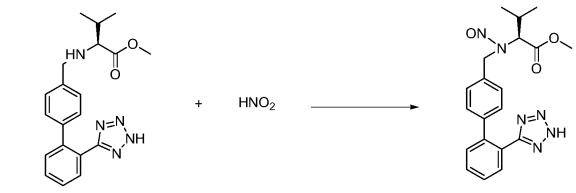
[0007] SUMMARY OF THE INVENTION

[0008] The inventors of the present application found during the development of the valsartan synthesis process that when DMF was used as a solvent, DMF was easily decomposed to produce dimethylamine during the high-temperature reaction. During the azide quenching process, dimethylamine It will react with nitrite to produce highly toxic N-nitrosodimethylamine (NDMA) impurities. If the valsartan methyl ester intermediate in the valsartan process is not separated first, the resulting N-nitrosodimethylamine Nitrodimethylamine (NDMA) impurities will remain in the valsartan API. The production process of NDMA is as follows:

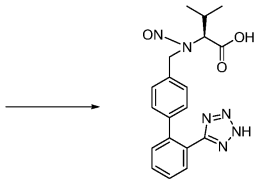
[0009] 

[0010] In addition, patent document CN103613558A also pointed out that in the process of quenching azide with nitrite under acidic conditions, a small amount of devaleryl impurities in the intermediate of valsartan methyl ester will react with nitrous acid to produce An N-nitroso compound will then be converted into valsartan impurity K in the subsequent process, and the production process is as follows:

[0011] —3/33—

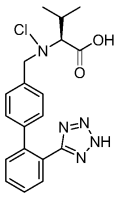


缬沙坦甲酯脱戊酰基杂质



缬沙坦杂质K

[0012] In this patent document, the improved strategy is to use sodium hypochlorite to replace sodium nitrite to quench azide; but the inventor of the present application found after further research that although the technical solution of this patent document can avoid the generation of impurity K, at the same time Another highly toxic valsartan N-chloride impurity may also be produced with the following structural formula:

[0013] 

缬沙坦N-氯代物 。

[0014] The inventors of the present application have further researched the synthesis process of valsartan and found that, before quenching the azide, the valsartan methyl ester intermediate is separated, which can avoid the high Possibility that impurities such as toxic N-nitrosodimethylamine (NDMA), valsartan impurity K and valsartan N-chloride are brought into the valsartan bulk drug; further, by optimizing other operating conditions, For example, controlling the water content in the solvent, the crystallization temperature, etc. during crystallization, to prepare a high-purity (without the above-mentioned impurities) valsartan product; the present invention is completed based on the above-mentioned findings.

[0015] The object of the present invention is to provide a kind of high-purity valsartan synthesis method, to synthesize non-toxic N-nitrosodimethylamine (NDMA), valsartan impurity K and valsartan N-chloride Valsartan such as impurities, the method comprises the following steps:

[0016] (1) synthesizing the valsartan methyl ester compound intermediate, thereby obtaining the reaction mixture containing the valsartan methyl ester compound intermediate;

[0017] In some specific embodiments of the present invention, the step (1) comprises: dissolving the valsartan cyanide intermediate in N,N-dimethylformamide (DMF), then adding azide and the first One acid, heating and stirring to carry out tetrazolium ring-forming reaction, synthesizing the valsartan methyl ester intermediate, thereby obtaining the reaction mixture containing the valsartan methyl ester intermediate;

[0018] (2) the reaction mixture is diluted with brine or water, and the first extraction solvent is added, and after heating, the valsartan methyl ester intermediate is extracted; The first organic layer; the first organic layer is washed at least once with brine or water, and the aqueous layer is separated to obtain the second organic layer containing the valsartan methyl ester intermediate;

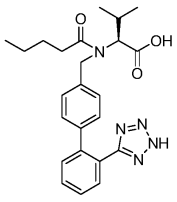
[0019] In some specific embodiments of the present invention, the water layers separated in step (2) can be combined, and the azide in the separated water layer can be quenched with a quencher under acidic conditions;

[0020] (3) in the second organic layer containing the valsartan methyl ester compound intermediate, add alkali solution, stir to carry out hydrolysis, stand for layering, after separating the organic layer, the water layer is adjusted to acidity with the second acid pH, Then add the second extraction solvent to the water layer to extract the valsartan compound, stand for stratification to obtain the third organic layer containing the valsartan compound; control the third organic layer by adding a desiccant or removing water by distillation When the solvent in the third organic layer is partially concentrated, or the solvent in the third organic layer is evaporated to dryness, after adding a new solvent, crystallize and filter to obtain the valsartan crude product;

[0021] In some specific embodiments of the present invention, the target value is 2% by mass, preferably 1%, more preferably 0.5%, and most preferably 0.35%;

[0022] (4) adding the valsartan crude product to the crystallization solvent, heating to dissolving, cooling after heat preservation for crystallization, filtering, and washing the filter cake with the crystallization solvent and drying to obtain the valsartan finished product.

[0023] Valsartan (Valsartan) mentioned in the present invention, its structural formula is as follows:

[0024] 

$C_{24}H_{29}N_5O_3$
Exact Mass: 435.227

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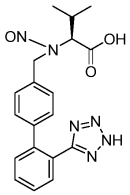
[0025] The N-nitrosodimethylamine (NDMA) mentioned in the present invention, its structural formula is as follows:

[0026] 

N-亚硝基二甲胺

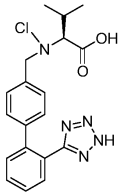
NDMA ;

[0027] Valsartan impurity K mentioned in the present invention, its structural formula is as follows:

[0028] 

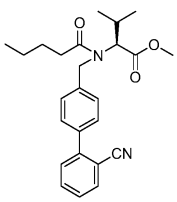
缬沙坦杂质K

[0029] Valsartan N-chloride mentioned in the present invention, its structural formula is as follows:

[0030] 

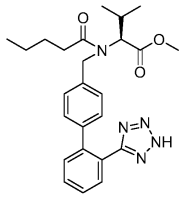
缬沙坦N-氯代物

[0031] In the present invention, valsartan cyanide intermediate structural formula is shown in I:

[0032] 

式 I;

[0033] In the present invention, the intermediate structural formula of valsartan methyl ester compound is shown in II:

[0034] 

式 II。

[0035] In some specific embodiments of the present invention, the azide in step (1) is selected from sodium azide, potassium azide, lithium azide, cesium azide and trimethylsilyl azide ($TMSN_3$) and the like or any combination thereof; preferably selected from sodium azide, potassium azide or trimethylsilyl azide ($TMSN_3$).

[0036] In some specific embodiments of the present invention, the first acid in step (1) is Lewis acid; preferably, the first acid is selected from triethylamine hydrohalide, triethylamine sulfate, triethylamine Hydrogen sulfate, triethylamine phosphate, triethylamine hydrogen phosphate, trimethylamine hydrohalide, trimethylamine sulfate, trimethylamine hydrogen sulfate, trimethylamine phosphate, trimethylamine hydrogen phosphate, diisopropyl Ethylamine hydrohalide, diisopropylethylamine sulfate, diisopropylethylamine hydrogen sulfate, diisopropylethylamine phosphate, pyridine hydrohalide, pyridine sulfate, pyridine hydrogen sulfate, pyridine phosphate, pyridine hydrogen phosphate, N-methylmorpholine hydrohalide, N-methylmorpholine sulfate, N-methylmorpholine hydrogen sulfate, N-methylmorpholine phosphate, N- Methylmorpholine hydrogen phosphate, N-methylpiperidine hydrohalide, N-methylpiperidine sulfate, N-methylpiperidine hydrogen sulfate, N-methylpiperidine phosphate, N-methylpiperidine Piperidine hydrogen phosphate, N-methyltetrahydropyrrole hydrohalide, N-methyltetrahydropyrrole sulfate, N-methyltetrahydropyrrole hydrogen sulfate, N-methyltetrahydropyrrole phosphate, N-methyltetrahydropyrrole hydrogen phosphate, tributyltin chloride, anhydrous zinc chloride, dihydrate zinc chloride, anhydrous titanium tetrachloride, etc., more preferably triethylamine hydrogen chloride, triethylamine One of sulfate, triethylamine hydrogen sulfate, pyridine hydrochloride and anhydrous zinc chloride or any combination thereof;

[0037] In the present invention, the temperature range of the tetrazolium cyclization reaction in step (1) is 70-180°C, more preferably 100-140°C.

[0038] In some specific embodiments of the present invention, the brine described in step (2) is selected from one of sodium chloride aqueous solution, magnesium chloride aqueous solution, potassium chloride aqueous solution, calcium chloride aqueous solution, sodium sulfate aqueous solution or any combination thereof , more preferably a saturated sodium chloride aqueous solution or a sodium chloride aqueous solution with a mass fraction of 10-20%.

[0039] In some specific embodiments of the present invention, the first extraction solvent described in step (2) is a solvent that can dissolve the valsartan methyl ester compound intermediate and is immiscible with water, preferably selected from toluene, xylene, xylene One or any combination of methyl chloride, methyl tert-butyl ether, isopropyl ether, n-butyl ether, anisole, phenethyl ether, n-hexyl ether, n-heptyl ether, more preferably toluene, xylene, methyl ether tert-butyl ether, anisole or n-butyl ether.

[0040] In some specific embodiments of the present invention, the heating temperature range during heating and extraction in step (2) is 35-140°C, preferably 45-100°C.

[0041] In some specific embodiments of the present invention, the quenching agent is selected from one of nitrite, hypochlorite or hypobromite or any combination thereof, preferably selected from sodium nitrite, nitrous acid One or any combination of potassium, sodium hypochlorite, sodium hypobromite, calcium hypobromite, calcium hypochlorite, etc., preferably selected from sodium nitrite or sodium hypochlorite.

[0042] In some specific embodiments of the present invention, when quenching the azide in the water layer, the acid used to form the acidic condition is an inorganic strong acid, preferably one of hydrochloric acid and sulfuric acid or a combination thereof; pH is adjusted after adding the acid Values range from 0-5, preferably 1-3.

[0043] In some specific embodiments of the present invention, when the azide in the water layer is quenched in step (2), the temperature range of the water layer is -5-40°C, preferably 5-20°C.

[0044] In some specific embodiments of the present invention, the alkaline solution described in step (3) is one or a combination of an aqueous hydroxide solution and an aqueous carbonate solution, more preferably an aqueous sodium hydroxide solution with a mass fraction of 30% Or a 30% potassium hydroxide aqueous solution.

[0045] In some specific embodiments of the present invention, the hydrolysis reaction is carried out with stirring after adding the alkali solution in step (3), and the temperature range of the hydrolysis reaction is -10-40°C, preferably 0-20°C; the reaction time range is 5-40 hours , preferably 15-25 hours.

[0046] In some specific embodiments of the present invention, in the step of adjusting the pH of the water layer to be acidic with a second acid described in step (3), the second acid used is an inorganic strong acid, preferably one of hydrochloric acid and sulfuric acid. or a combination thereof; after adding acid, the pH value is adjusted in the range of 0.5-6, preferably 1-3.

[0047] In some specific embodiments of the present invention, the second extraction solvent used in step (3) is a solvent that can be layered with the water layer, preferably ethyl acetate or methyl tert-butyl ether.

[0048] In some specific embodiments of the present invention, the new solvent described in step (3) is a single solvent that can dissolve valsartan and a mixture of multiple solvents, preferably selected from ethyl acetate, acetone, ethanol, isopropanol Or a mixed solvent of ethyl acetate and dichloromethane; more preferably, in the mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1:3 to 3:1.

[0049] In some specific embodiments of the present invention, the desiccant described in step (3) is selected from one of anhydrous chloride metal salt, anhydrous sulfate metal salt or a combination thereof, preferably selected from anhydrous magnesium sulfate or anhydrous sodium sulfate.

[0050] In some specific embodiments of the present invention, the crystallization solvent described in step (4) is a single solvent or a mixed solvent of multiple solvents that can dissolve valsartan, preferably ethyl acetate or ethyl acetate and dichloromethane more preferably, in the mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1:3 to 3:1.

[0051] The method for synthesizing valsartan provided by the present invention, by separating the valsartan methyl ester intermediate before the quenching treatment of the azide, avoids the highly toxic N-suboxide produced in the azide quenching process from the process source. Impurities such as nitrodimethylamine (NDMA), valsartan impurity K and valsartan N-chloride are brought into the valsartan methyl ester compound intermediate, and then bring into the possibility of the valsartan crude drug, thereby Ensure the safety of valsartan medication.

Detailed ways

[0052] In order to make the purpose, technical solutions and advantages of the present invention more clear, the following examples are given to further describe the present invention in detail. Obviously, the described embodiments are only some, but not all, embodiments of the present invention. Based on the embodiments of the present invention, all other embodiments obtained by those of ordinary skill in the art without creative efforts shall fall within the protection scope of the present invention.

[0053] Synthetic Example of Valsartan

[0054] In the following examples and comparative examples of the present invention, the N-nitrosodimethylamine (NDMA) in the finished valsartan was detected by GC-MS, and the finished valsartan was detected by LC-MS. The valsartan impurity K and valsartan N-chloride in the valsartan are detected; First, the GC-MS (gas chromatography-mass spectrometry) and LC-MS (liquid phase) adopted to the following examples of the present invention and comparative examples Chromatography-mass spectrometry) test method will be described.

[0055] 1. Chromatographic conditions and detection methods of GC-MS:

[0056] Instrument: ThermoFischer gas chromatography single quadrupole mass spectrometer (Trace 1300 & ISQLT)

[0057] Chromatographic column: DB-1701, 60m×0.32mm, 1.8μm (14% cyanopropylphenyl-86% dimethylpolysiloxane copolymer)

[0058] Carrier Gas: Helium

[0059] Line speed: 1.0mL/min

[0060] Inlet temperature: 180℃

[0061] Injection volume: 2.0 μL

[0062] Split ratio: 25:1

[0063] Warming program:

[0064] The initial temperature was 60°C, kept for 2min, then heated to 240°C at a rate of 15°C/min, and kept for 5min

[0065] Ion source mode: EI, positive ion

[0066] Ion source: 250℃

[0067] Quadrupole temperature: 160℃

[0068] Relative voltage: 200V

[0069] Scan Mode: Single Ion Extraction Mode (SIM)

[0070] SIM ion current: m/z 74.0

[0071] Diluent: DMSO

[0072] Blank solution: same as diluent;

[0073] Preparation of standard solution of N-nitrosodimethylamine (NDMA) reference substance: Weigh an appropriate amount of N-nitrosodimethylamine (NDMA) reference substance, and dilute it with diluent to the concentration of NDMA: 0.2, 0.8, 3.2, 6.4, 20 μg/mL, shake until completely dissolved before use.

[0074] Detection of N-nitrosodimethylamine (NDMA) content in the sample to be tested (valsartan finished product prepared by the following examples and comparative examples):

[0075] Weigh 400 mg of the sample to be tested, accurately weigh it into a 20 mL headspace vial, and then accurately pipette 2 mL of the diluent, shake to dissolve, and mix to serve as the test solution. Use the above-mentioned GC-MS method to detect the NDMA standard solution of the test solution and different concentrations, and calculate the NDMA content in the sample to be tested by the standard curve method;

[0076] 2. Chromatographic conditions and detection methods of LC-MS:

[0077] Instrument: Agilent LC-QTOF high precision liquid mass spectrometer (Agilent 6120&6545)

[0078] Chromatographic column: Waters Symmetry C8, 250×4.6mm; 5μm

[0079] Mobile phase A: 0.1% formic acid in water

[0080] Mobile Phase B: Acetonitrile

[0081] Column temperature: 35℃

[0082] Injection volume: 10μL

[0083] Detection wavelength: 230nm (DAD spectrum 200-400nm full scan)

[0084] Gradient table:

[0085]

时间(min)	流动相 A(%V/V)	流动相 B(%V/V)	流速（mL/min）
0	50	50	1.2
4	50	50	1.2
16	20	80	1.2
24	20	80	1.2
26	50	50	1.2
35	50	50	1.2

[0086] Ion source: ESI ion source

[0087] Mass spectrometer parameters:

[0088]

质谱检测器参数

干燥气体流速	6 L/min	MS_1 扫描模式	Full scan
干燥气体温度	325 ℃	MS_1 扫描时间	5~40 min
雾化气体压力	35 psi	MS_1 扫描范围	*m/z* 100-1700
毛细管电压	+3500 V	鞘气流速	12 L/min
离子模式	ESI 正离子	鞘气温度	350℃
碎片电压	90 V	目标离子 1	*m/z* 381.167（缬沙坦杂质 K）
目标离子 2	*m/z* 386.138（缬沙坦 N-氯代物）	离子抽提误差	10 ppm

[0089] Preparation of standard solution of valsartan impurity K reference substance: Weigh an appropriate amount of valsartan impurity K reference substance, and dilute with diluent (0.1% formic acid aqueous solution: acetonitrile=2:1 (v/v)) to the concentrations: 0.2, 0.8, 3.2, 6.4, 20 μg/mL, shake until completely dissolved before use.

[0090] Preparation of standard solution of valsartan N-chloride reference substance: Weigh an appropriate amount of valsartan N-chloride reference substance, and dilute it with diluent (0.1% formic acid aqueous solution: acetonitrile = 2:1) to the concentrations: 0.2, 0.8, 3.2, 6.4, 20 μg/mL, shake until completely dissolved before use.

[0091] Detection of valsartan impurity K content in the sample to be tested: Weigh 400 mg of the sample to be tested, accurately weigh it into a 20 mL headspace bottle, and then accurately pipette 2 mL of diluent (0.1% formic acid aqueous solution: acetonitrile = 2:1), shake Shake to dissolve, mix well, as the test solution. The test solution and the standard solution of valsartan impurity K with different concentrations were detected by the above-mentioned LC-MS method, and the content of valsartan impurity K was calculated by the standard curve method.

[0092] Detection of valsartan N-chloride content in the sample to be tested: Weigh 400 mg of the sample to be tested, accurately weigh it into a 20 mL headspace bottle, and then accurately pipette 2 mL of diluent (0.1% formic acid aqueous solution: acetonitrile = 2:1) , shake to dissolve, mix, as the test solution. The test solution and standard solutions of valsartan N-chloride with different concentrations were detected by the above LC-MS method, and the content of valsartan N-chloride was calculated by the standard curve method.

[0093] Example 1

[0094] Synthesis of Valsartan

[0095] Add 100mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 70g of valsartan cyanide intermediate) to the reaction flask, followed by adding 36g of anhydrous zinc chloride and 25g of sodium azide, be heated to 125 ~ 135 ℃ and stir the reaction for 28 hours, after the reaction finishes, cool down to 45 ~ 48 ℃, then add 500mL methyl tertiary butyl ether and 400mL 20% (w/w) chlorine Aqueous sodium chloride solution, stirred for 1 hour at 45-48 ℃, stopped stirring, allowed to stand for stratification, separated the aqueous layer, and added 200 mL of saturated brine to the organic layer at 45-48 ℃, continued washing and stirring for 2 hours, separated the water layer, organic layer The layer was further washed with 200 mL of saturated brine at the same temperature and stirred for 2.5 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0096] Transfer the above-mentioned last separated organic layer to another reaction flask, cool to 10 ~ 15℃, then add 55mL of 30% (w/w) NaOH aqueous solution and 105mL of water, stir and react for 15 ~ 20 hours, stand to separate the base tert-butyl ether layer, the temperature of the water layer was further reduced to 0 ~ 10 ° C, 4mol/L hydrochloric acid solution was added dropwise to a pH value of 1 ~ 2, then 600 mL of ethyl acetate was added, and the water layer was separated after stirring for 30 minutes. , then steamed 350 mL of ethyl acetate under reduced pressure at 40 ° C, if the moisture content was higher than 0.4%, continued to add 200 mL of fresh ethyl acetate (the moisture content was lower than 0.01% (w/w)), and then at 40 ° C 200 mL of ethyl acetate was evaporated under reduced pressure until the moisture content was less than or equal to 0.4 (w/w)% (the final moisture content was 0.35% (w/w)), cooled to 0 to 10° C., crystallized for 10 hours, and filtered. The crude valsartan product is obtained, and it is directly put into the crystallization process of the finished valsartan product without drying.

[0097] The valsartan crude product obtained in the previous step was put into the reaction flask, then 400 mL of ethyl acetate was added, the temperature was raised to 35 ~ 40 ℃ and stirred until the dissolution was clarified, then slowly cooled to 10 ~ 20 ℃, continued crystallization for 2 hours, stopped stirring, Filtration, followed by washing with 30 mL of ethyl acetate at 10-15° C., and drying to obtain 63.g of valsartan finished product with a yield of 85%.

[0098] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were detected, and the detection results were all undetected (the impurity concentration was lower than the sensitivity of the detection method, and no peak appeared).

[0099] Quenching of azide

[0100] Transfer the previously combined water layer to the reaction flask, add 13g of sodium nitrite, cool to 15°C, then slowly add 90mL of 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0101] Example 2

[0102] Synthesis of Valsartan

[0103] Add 100mL of the N,N-dimethylformamide (DMF) solution of the valsartan cyanide intermediate (containing 60g of the valsartan cyanide intermediate) to the reaction flask, followed by adding 34g of anhydrous zinc chloride and 29g of potassium azide, heat up to 135 ~ 140 ℃ and stir for 20 hours, after the reaction, cool down to 90 ~ 100 ℃, then add 600mL n-butyl ether and 460mL 20% (w/w) sodium chloride Aqueous solution, stirred at 90 ~ 100℃ for 3 hours, stop stirring, stand for stratification, separate the water layer, add 200mL of saturated brine to the organic layer at 90 ~ 100℃, continue to wash and stir for 2 hours, separate the water layer, and the organic layer again. Washing and stirring were continued with 200 mL of saturated brine at the same temperature for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0104] Transfer the above-mentioned last separated organic layer to another reaction flask, cool to 10-15°C, then add 50 mL of 30% (w/w) NaOH aqueous solution and 100 mL of water, stir and react for 15-20 hours, stand for separation Butyl ether layer, the temperature of the water layer was further reduced to 0-10 ° C, 4 mol/L sulfuric acid solution was added dropwise to a pH value of 1-3, then 550 mL of ethyl acetate was added, stirred for 30 minutes, the water layer was separated, and then added 50g of anhydrous magnesium sulfate was stirred for 2 hours until the moisture content was 0.2%, filtered to remove magnesium sulfate, then 340 mL of ethyl acetate was evaporated under reduced pressure at 40 ° C, cooled to 0 to 5 ° C, crystallized for 8 hours, and filtered to obtain valerian. Crude sartan is directly put into the crystallization process of valsartan without drying.

[0105] The valsartan crude product obtained in the previous step was put into the reaction flask, then 300 mL of ethyl acetate was added, the temperature was raised to 40 ~ 42°C and stirred until the dissolution was clarified, then slowly cooled to 0 ~ 5°C, continued crystallization for 2 hours, and stopped stirring, Filtration, followed by washing with 30 mL of ethyl acetate at 0-2° C., and drying to obtain 55.3 g of finished valsartan, with a yield of 86%.

[0106] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0107] Quenching of azide

[0108] Transfer the previously combined water layer to the reaction flask, add 12g of sodium hypochlorite, adjust the temperature to 20°C, then slowly add 120mL of 2mol/L dilute sulfuric acid solution dropwise, continue stirring for 30 minutes, then the azide can be quenched; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0109] Example 3

[0110] Synthesis of Valsartan

[0111] Add 130mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80g of valsartan cyanide intermediate) to the reaction flask, followed by adding 45g of anhydrous zinc chloride and 30g of sodium azide, be warming up to 130 ~ 135 ℃ and stir the reaction for 24 hours, after the reaction finishes, be cooled to 90 ~ 100 ℃, then add 440mL toluene and 440mL 20% (w/w) sodium chloride aqueous solution, 90 Stir for 2 hours at ~100 °C, stop stirring, stand for stratification, separate the aqueous layer, add 220 mL of saturated brine to the organic layer at 90 ~ 100 °C, continue to wash and stir for 2 hours, separate the water layer, and then add the organic layer to the same The mixture was further washed and stirred with 220 mL of saturated brine at the temperature for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0112] The organic layer finally separated was transferred to another reaction flask, cooled to 10-15° C., then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature was further reduced to 0 ~ 10℃, 6mol/L hydrochloric acid solution was added dropwise to pH 1 ~ 2, then 700mL ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then steamed under reduced pressure at 40℃ 400 mL of ethyl acetate, if the moisture content is higher than 0.5%, continue to add 200 mL of fresh ethyl acetate (the moisture content is lower than 0.01%), and then evaporate 200 mL of ethyl acetate under reduced pressure at 40°C until the moisture content is lower than 0.01%. or equal to 0.5% (the final moisture content is 0.28%), cooled to 0 ~ 10 DEG C, crystallized for 10 hours, filtered to obtain the crude valsartan product, and directly put into the crystallization process of the finished valsartan product without drying.

[0113] Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, be warming up to 40 ~ 45 ℃ and stir until the dissolution is clarified, then slowly cool down to -5 ~ 5 ℃, continue to crystallize for 2 hours, stop stirring , filtered, and then washed with 50 mL of ethyl acetate at 0 to 2° C., and dried to obtain 75.6 g of valsartan finished product with a yield of 87%.

[0114] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0115] Quenching of azide

[0116] Transfer the previously merged water layer to the reaction flask, add 15g of sodium nitrite, cool to 10°C, then slowly add 120mL of 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0117] Example 4

[0118] Synthesis of Valsartan

[0119] Add 250mL of the N,N-dimethylformamide (DMF) solution of the valsartan cyanide intermediate (containing 160g of the valsartan cyanide intermediate) to the reaction flask, followed by adding 92g of anhydrous zinc chloride and 106g of trimethylsilyl azide ($TMSN_3$), heated to 130 ~ 135°C and stirred for 28 hours, after the reaction was completed, the temperature was lowered to 90 ~ 100°C, then 800mL of xylene and 850mL of 20% (w/w) were added.) aqueous sodium chloride solution, stirred at 90 ~ 100°C for 2 hours, stopped stirring, left to stand for stratification, separated the aqueous layer, the organic layer was added with 450 mL of saturated brine at 90 ~ 100°C and continued to be washed and stirred for 3 hours, and the aqueous layer was separated , the organic layer was further washed with 450 mL of saturated brine at the same temperature and stirred for 3 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0120] Transfer the above-mentioned last separated organic layer to another reaction flask, cool to 10 ~ 15°C, then add 130mL 30% (w/w) NaOH aqueous solution and 280mL water, stir and react for 14 ~ 18 hours, stand to separate out two Toluene layer, the temperature of the water layer was further reduced to -5 ~ 0 ℃, 6mol/L hydrochloric acid solution was added dropwise to a pH value of 1.0 ~ 2.0, then 1500 mL of ethyl acetate was added, stirred for 30 minutes, the water layer was separated, and then at 40 900 mL of ethyl acetate was evaporated under reduced pressure at ℃. If the moisture content was higher than 0.3%, 200 mL of fresh ethyl acetate was added (the moisture content was lower than 0.01%), and then 200 mL of ethyl acetate was evaporated under reduced pressure at 40 °C. , until the moisture content is lower than 0.3% (final moisture content is 0.25%), cooled to -5 ~ 0 ℃, crystallized for 12 hours, filtered to obtain the valsartan crude product, and directly put into the valsartan finished product crystallization process without drying.

[0121] The valsartan crude product obtained in the previous step was put into the reaction flask, then 1000 mL of ethyl acetate was added, the temperature was raised to 40 ~ 45°C and stirred until the dissolution was clarified, then slowly cooled to 0 ~ 3°C, continued crystallization for 3 hours, and stopped stirring, Filtration, followed by washing with 80 mL of ethyl acetate at 0-2° C., and drying to obtain 150.8 g of finished valsartan, with a yield of 88%.

[0122] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0123] Quenching of azide

[0124] Transfer the previously combined water layer to the reaction flask, add 30g of sodium nitrite, cool to 15°C, then slowly dropwise add 200mL of 3mol/L dilute sulfuric acid solution, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0125] Example 5

[0126] Synthesis of Valsartan

[0127] To the reaction flask, add 130 mL of the N,N-dimethylformamide (DMF) solution of the valsartan cyanide intermediate (containing 80 g of the valsartan cyanide intermediate), and then add 48 g of triethylamine hydrochloride Salt and 30g of sodium azide were heated to 120 ~ 125°C and stirred for 28 hours. After the reaction, the temperature was lowered to 90 ~ 100°C, then 450mL of toluene and 200mL of water were added, stirred at 90°C for 2 hours, and the stirring was stopped. Let stand for stratification, separate the aqueous layer, add 260 mL of saturated brine to the organic layer at 90 to 100°C, continue to wash and stir for 2 hours, separate the aqueous layer, and continue to wash and stir the organic layer with 260 mL of saturated brine at the same temperature. After 2 hours, the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0128] The organic layer finally separated was transferred to another reaction flask, cooled to 5 ~ 10° C., then 65mL of 30% NaOH aqueous solution and 140mL of water were added, and the reaction was stirred for 20 to 25 hours. The temperature was further lowered to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 1-3, then 700mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then 400mL was evaporated under reduced pressure at 40°C Ethyl acetate, if the moisture content is higher than 0.5%, continue to add 200 mL of fresh ethyl acetate (the moisture content is lower than 0.01%), and then evaporate 200 mL of ethyl acetate under reduced pressure at 40°C until the moisture content is lower than or is equal to 0.5% (final moisture content is 0.25%), cooled to 0 ~ 10 DEG C, crystallized for 10 hours, filtered to obtain crude valsartan, and directly put into the crystallization process of valsartan finished product without drying.

[0129] The valsartan crude product obtained in the previous step was dropped into the reaction flask, then 700 mL of ethyl acetate-dichloromethane mixed solution (volume ratio was 2:1) was added, and the temperature was raised to 40 ~ 45 ° C and stirred until the dissolution was clarified, and then slowly lowered the temperature At -5 ~ 5°C, continue to crystallize for 2 hours, stop stirring, filter, and then wash with 50 mL of ethyl acetate at 0 ~ 2°C, and dry to obtain 69.4 g of finished valsartan with a yield of 81%.

[0130] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0131] Quenching of azide

[0132] Transfer the previously merged water layer to the reaction flask, add 20g potassium nitrite, cool to 10°C, then slowly add 120mL 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0133] Example 6

[0134] Synthesis of Valsartan

[0135] To the reaction flask, add 130 mL of the N,N-dimethylformamide (DMF) solution of the valsartan cyanide intermediate (containing 80 g of the valsartan cyanide intermediate), followed by adding 42 g of triethylamine sulfate and 50g of trimethylsilyl azide ($TMSN_3$), be warming up to 110 ~ 120 ℃ under stirring reaction 35 hours, after the reaction finishes, be cooled to 90 ~ 100 ℃, then add 500mL toluene and 500mL 20% sodium chloride aqueous solution, Stir at 90°C for 2 hours, stop stirring, let stand for stratification, separate the water layer, add 250 mL of saturated brine to the organic layer at 90-100°C, continue washing and stirring for 2 hours, separate the water layer, and the organic layer at the same temperature again The mixture was further washed with 250 mL of saturated brine and stirred for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0136] The organic layer finally separated was transferred to another reaction flask, cooled to 5-10°C, then 60mL of 30% NaOH aqueous solution and 120mL of water were added, and the reaction was stirred for 20-25 hours. The temperature was further reduced to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 2-3, then 700mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, the water layer was separated after stirring for 30 minutes, and then Add 80 g of anhydrous sodium sulfate and stir for 2 hours until the moisture content is 0.18%, filter, remove the sodium sulfate, steam 400 mL of ethyl acetate under reduced pressure at 40 ° C, cool to 0 ~ 5 ° C, crystallize for 8 hours, and filter to obtain The crude valsartan product is directly put into the crystallization process of the finished valsartan product without drying.

[0137] The valsartan crude product obtained in the previous step is dropped into the reaction flask, then 1000 mL of ethyl acetate-dichloromethane mixed solution (volume ratio is 1:1) is added, and the temperature is raised to 40 ~ 45 ° C and stirred until the dissolution is clarified, and then the temperature is slowly lowered. To -5 ~ 5 ℃, continue to crystallize for 2 hours, stop stirring, filter, then wash with 100 mL of 0 ~ 2 ℃ ethyl acetate-dichloromethane mixture (volume ratio is 1:1), and dry to obtain valsartan The finished product is 62.6 g, and the yield is 73%.

[0138] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0139] Quenching of azide

[0140] Transfer the previously combined water layer to the reaction flask, add 13 g of calcium hypochlorite, cool to 10 ° C, then slowly dropwise add 100 mL of a 3mol/L dilute sulfuric acid solution, continue stirring for 30 minutes, the azide can be quenched ; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0141] Example 7

[0142] Synthesis of Valsartan

[0143] Add 250mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 160g of valsartan cyanide intermediate) into the reaction flask, followed by adding 130g of triethylamine hydrogen sulfate Salt and 106 g of trimethylsilyl azide ($TMSN_3$) were heated to 130-135° C. and stirred for 28 hours. After the reaction was completed, the temperature was lowered to 75-85° C., and then 800 mL of anisole and 500 mL of 10% chlorinated solution were added. Aqueous sodium solution, stirred at 75-85 ℃ for 2 hours, stopped stirring, allowed to stand for stratification, separated the aqueous layer, added 450 mL of saturated brine to the organic layer at 75-85 ℃, continued to wash and stirred for 3 hours, separated the aqueous layer and the organic layer At the same temperature, the mixture was further washed with 450 mL of saturated brine and stirred for 3 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0144] The organic layer finally separated above was transferred to another reaction flask, cooled to 10-15° C., then 130 mL of 30% NaOH aqueous solution and 280 mL of water were added, and the reaction was stirred for 14 to 18 hours. The temperature of the water layer was further reduced to -5 ~ 0°C, 6mol/L hydrochloric acid solution was added dropwise to a pH value of 1.5 ~ 2.5, then 1500mL ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then the pressure was reduced at 40°C All the ethyl acetate was evaporated, then 600 mL of acetone was added, the temperature was raised to 40 ° C and all dissolved, the final moisture content was 0.17%, slowly cooled to 0 to 5 ° C, crystallized for 12 hours, filtered to obtain the crude valsartan, directly without drying Put into the crystallization process of valsartan finished product.

[0145] The valsartan crude product obtained in the previous step was put into the reaction flask, then 1000 mL of ethyl acetate was added, the temperature was raised to 40 ~ 45°C and stirred until the dissolution was clarified, then slowly cooled to 0 ~ 3°C, continued crystallization for 3 hours, and stopped stirring, Filtration, followed by washing with 80 mL of ethyl acetate at 0-2° C., and drying to obtain 140.6 g of finished valsartan, with a yield of 82%.

[0146] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0147] Quenching of azide

[0148] Transfer the previously combined water layer to the reaction flask, add 30g of sodium nitrite, cool to 15°C, then slowly add 180mL of 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes, then the azide can be quenched ; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0149] Example 8

[0150] Synthesis of Valsartan

[0151] Add 130mL of valsartan cyanide intermediate N,N-dimethylformamide (DMF) solution (containing 80g of valsartan cyanide intermediate) into the reaction flask, then add 95g of pyridine hydrochloride and 30g of sodium azide was heated to 130 ~ 140°C and stirred for 24 hours. After the reaction was finished, the temperature was lowered to 90 ~ 100°C, then 440mL of toluene and 440mL of 20% aqueous magnesium chloride were added, and the stirring was stopped for 2 hours at 90°C. , stand for stratification, separate the water layer, add 300 mL of saturated aqueous magnesium chloride solution to the organic layer at 90 to 100 ° C and continue to wash and stir for 2 hours, separate the water layer, and then continue to wash the organic layer with 300 mL of saturated aqueous magnesium chloride solution at the same temperature. After stirring for 2 hours, the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0152] The organic layer finally separated was transferred to another reaction flask, cooled to 10-15° C., then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature was further reduced to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 2-3, then 700mL ethyl acetate was added, and the water layer was separated after stirring for 30 minutes, and then all was evaporated under reduced pressure at 40°C. ethyl acetate, then add 500mL of isopropanol, be warming up to 40 °C and all dissolved, the final moisture content is 0.15%, cooled to 0 ~ 10 °C, crystallized for 10 hours, filtered to obtain the crude valsartan, directly put into valsartan without drying Sartan finished product crystallization process.

[0153] The valsartan crude product obtained in the previous step was put into the reaction flask, then 540 mL of ethyl acetate was added, the temperature was raised to 40 ~ 45°C and stirred until the dissolution was clarified, then slowly cooled to -5 ~ 5°C, continued to crystallize for 2 hours, and stopped stirring , filtered, and then washed with 50 mL of ethyl acetate at 0 to 2° C., and dried to obtain 80.0 g of valsartan finished product with a yield of 84%.

[0154] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0155] Quenching of azide

[0156] Transfer the previously combined water layer to the reaction flask, add 35g of sodium hypobromite, cool to 10°C, then slowly dropwise add 120mL of 3mol/L dilute hydrochloric acid solution, continue stirring for 30 minutes, and then the azide can be quenched ; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0157] Example 9

[0158] Synthesis of Valsartan

[0159] Add 100mL of the N,N-dimethylformamide (DMF) solution of the valsartan cyanide intermediate (containing 60g of the valsartan cyanide intermediate) to the reaction flask, followed by adding 34g of anhydrous zinc chloride and the sodium azide of 25g, be warming up to 130 ~ 135 °C of lower stirring reaction 28 hours, after the reaction finishes, be cooled to 60 ~ 70 °C, then add 1000mL anisole and 460mL 20% sodium sulfate aqueous solution, under 60 ~ 70 °C Stir for 3 hours, stop stirring, stand for stratification, separate the water layer, add 200 mL of saturated aqueous sodium sulfate solution to the organic layer at 60-70 ° C, continue to wash and stir for 2 hours, separate the water layer, and then use the organic layer at the same temperature. 200 mL of saturated aqueous sodium sulfate solution was continuously washed and stirred for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0160] The organic layer finally separated was transferred to another reaction flask, cooled to 5-10° C., then 60 mL of 30% NaOH aqueous solution and 100 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature of the water layer was further reduced to 0 to 10°C, 6mol/L hydrochloric acid solution was added dropwise to a pH value of 1 to 3, then 550 mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then 50 g of anhydrous magnesium sulfate was added to stir After 2 hours, to a moisture content of 0.21%, filter, remove magnesium sulfate, steam 340 mL of ethyl acetate under reduced pressure at 40 °C, cool to 0 to 5 °C, crystallize for 8 hours, and filter to obtain crude valsartan without drying. Directly put into the crystallization process of valsartan finished product.

[0161] The valsartan crude product obtained in the previous step was put into the reaction flask, then 300 mL of ethyl acetate was added, the temperature was raised to 40 ~ 42°C and stirred until the dissolution was clarified, then slowly cooled to 0 ~ 5°C, continued crystallization for 2 hours, and stopped stirring, Filtration, followed by washing with 30 mL of ethyl acetate at 0-2° C., and drying to obtain 57.2 g of finished valsartan with a yield of 89%.

[0162] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0163] Quenching of azide

[0164] Transfer the previously combined water layer to the reaction flask, add 12g of sodium hypochlorite, adjust the temperature to 20°C, then slowly add 120mL of 2mol/L dilute sulfuric acid solution dropwise, continue stirring for 30 minutes, then the azide can be quenched; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0165] Example 10

[0166] Synthesis of Valsartan

[0167] Add 130mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80g of valsartan cyanide intermediate) to the reaction flask, followed by adding 45g of anhydrous zinc chloride and the sodium azide of 30g, be warming up to 130 ~ 140 °C of lower stirring reaction 24 hours, after the reaction finishes, be cooled to 80 ~ 90 °C, then add 500mL xylene and 440mL 20% sodium chloride aqueous solution, under 80 ~ 90 °C Stir for 2 hours, stop stirring, stand for stratification, separate the water layer, add 220 mL of saturated brine to the organic layer at 80-90 ° C, continue to wash and stir for 2 hours, separate the water layer, and then use 220 mL of the organic layer at the same temperature. The saturated brine was continuously washed and stirred for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0168] The organic layer finally separated was transferred to another reaction flask, cooled to 10-15° C., then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature of the layer was further reduced to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 1-2, then 700mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then evaporated under reduced pressure at 40°C. 400 mL

of ethyl acetate, if the moisture content is higher than 0.5%, continue to add 200 mL of fresh ethyl acetate (the moisture content is lower than 0.01%), and then evaporate 200 mL of ethyl acetate under reduced pressure at 40°C to a moisture content of 0.24 %, cooled to 5-8 DEG C, crystallized for 10 hours, filtered to obtain crude valsartan, and directly put into the crystallization process of finished valsartan without drying.

[0169] The valsartan crude product obtained in the previous step is dropped into the reaction flask, then 900 mL of ethyl acetate-dichloromethane mixed solution (volume ratio is 1:3) is added, and the temperature is raised to 40 ~ 45 ° C and stirred until the dissolution is clarified, and then the temperature is slowly lowered. To 5 ~ 10 ℃, continue to crystallize for 2 hours, stop stirring, filter, then wash with 90 mL of 5 ~ 8 ℃ ethyl acetate-dichloromethane mixed solution (volume ratio is 1:3), and dry to obtain finished valsartan 71.1 g, 83% yield.

[0170] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0171] Quenching of azide

[0172] Transfer the previously combined water layer to the reaction flask, add 35g calcium hypobromite, cool to 10°C, then slowly dropwise add 120mL 3mol/L dilute hydrochloric acid solution, continue stirring for 30 minutes, the azide can be quenched ; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0173] Example 11

[0174] Synthesis of Valsartan

[0175] Add 130mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80g of valsartan cyanide intermediate) to the reaction flask, followed by adding 45g of anhydrous zinc chloride and the sodium azide of 30g, be warming up to 130 ~ 140 ℃ of lower stirring reaction 24 hours, after the reaction finishes, be cooled to 60 ~ 70 ℃, then add 600mL n-butyl ether and 440mL 20% sodium chloride aqueous solution, 60 ~ 70 Stir at ℃ for 3 hours, stop stirring, stand for stratification, separate the aqueous layer, add 220 mL of saturated brine to the organic layer at 60-70 ℃, continue to wash and stir for 2 hours, separate the water layer, and then at the same temperature for the organic layer. The mixture was further washed with 220 mL of saturated brine and stirred for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined for the subsequent azide quenching procedure.

[0176] Transfer the organic layer finally separated to another reaction flask, cool to 5 ~ 10°C, then add 90mL 30% KOH aqueous solution and 150mL water, stir and react for 18 ~ 23 hours, stand to separate the n-butyl ether layer, The temperature of the water layer was further reduced to 0-10°C, 6 mol/L hydrochloric acid solution was added dropwise until the pH value was 2-3, then 700 mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then 50 g of anhydrous magnesium sulfate was added. Stir for 2 hours until the moisture content is 0.2%, filter, remove magnesium sulfate, steam 340 mL of ethyl acetate under reduced pressure at 40 ° C, cool down to 0 ~ 10 ° C, crystallize for 10 hours, and filter to obtain crude valsartan. Dry and directly put into the crystallization process of valsartan finished product.

[0177] The valsartan crude product obtained in the previous step was put into the reaction flask, then 540 mL of ethyl acetate was added, the temperature was raised to 40 ~ 45°C and stirred until the dissolution was clarified, then slowly cooled to -5 ~ 5°C, continued to crystallize for 2 hours, and stopped stirring , filtered, then washed with 50 mL of ethyl acetate at 0-2° C., and dried to obtain 65.1 g of valsartan finished product, with a yield of 76%.

[0178] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0179] Quenching of azide

[0180] Transfer the previously merged water layer to the reaction flask, add 15g of sodium nitrite, cool to 10°C, then slowly add 120mL of 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0181] Example 12

[0182] Synthesis of Valsartan

[0183] Add 130mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80g of valsartan cyanide intermediate) to the reaction flask, followed by adding 45g of anhydrous zinc chloride and the sodium azide of 30g, be warming up to 130 ~ 135 ℃ of lower stirring reaction 22 hours, after the reaction finishes, be cooled to 75 ~ 80 ℃, then add 500mL toluene and 400mL 20% sodium chloride aqueous solution, stir at 75 ~ 80 ℃ For 2 hours, stop stirring, stand for stratification, separate the aqueous layer, add 200 mL of saturated brine to the organic layer at 75-80 ° C, continue to wash and stir for 2 hours, separate the water layer, and then use 200 mL of the organic layer at the same temperature. The mixture was further washed with saturated brine and stirred for 2 hours, and the organic layer was separated. The aqueous layers separated from the three runs were combined and used for the subsequent azide quenching procedure.

[0184] The organic layer finally separated was transferred to another reaction flask, cooled to 10-15° C., then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature was further lowered to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 1-2, then 700mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then all was evaporated under reduced pressure at 40°C. ethyl acetate, then add 400mL of isopropanol, be warming up to 40 ℃ and completely dissolve (final moisture content is 0.21%), be cooled to 0 ~ 10 ℃, crystallize for 10 hours, filter to obtain the crude valsartan, directly drop into it without drying Crystallization process of valsartan finished product.

[0185] Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, be warming up to 40 ~ 45 ℃ and stir until the dissolution is clarified, then slowly cool down to -5 ~ 5 ℃, continue to crystallize for 2 hours, stop stirring , filtered, and then washed with 50 mL of ethyl acetate at 0 to 2° C., and dried to obtain 70.3 g of valsartan finished product with a yield of 82%.

[0186] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. Substitutes were tested, and the test results were all undetectable.

[0187] Quenching of azide

[0188] Transfer the previously merged water layer to the reaction flask, add 15g of sodium nitrite, cool to 10°C, then slowly add 120mL of 3mol/L dilute hydrochloric acid solution dropwise, continue stirring for 30 minutes to quench the azide; After further concentration and desalination, the waste water can be discharged into the low-concentration waste water tank for further treatment.

[0189] Comparative Example 1

[0190] Add 130mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 80g of valsartan cyanide intermediate) to the reaction flask, followed by adding 45g of anhydrous zinc chloride and the sodium azide of 30g, be warming up to 130 ~ 135 ℃ of lower stirring reaction 24 hours, after the reaction finishes, be cooled to 30 ~ 50 ℃, then add 50mL DMF, 3000mL methyl tertiary butyl ether and 200mL water, 30 ~ 50 Stir for 1 hour at ℃, cool to 0 ~ 10°C, then add 12g sodium nitrite, stir for

30min, slowly add 110mL 6mol/L dilute hydrochloric acid solution dropwise under stirring state at 0 ~ 10°C until the pH value of the solution is 1 ~ 2, static set, and the organic layer was separated.

[0191] The organic layer separated above was transferred to another reaction flask, cooled to 10-15° C., then 65 mL of 30% NaOH aqueous solution and 140 mL of water were added, and the reaction was stirred for 15 to 20 hours. Lower to 0 ~ 10°C, add 6mol/L hydrochloric acid solution dropwise until pH value is 1 ~ 2, then add 700mL ethyl acetate, stir for 30 minutes, separate the water layer, then evaporate 400mL ethyl acetate under reduced pressure at 40°C Ester, if the moisture content is higher than 0.5%, continue to add 200 mL of fresh ethyl acetate (the moisture content is lower than 0.01%), and then evaporate 200 mL of ethyl acetate under reduced pressure at 40°C until the moisture content is lower than or equal to 0.5 % (the final moisture content is 0.28%), cooled to 0-10° C., crystallized for 10 hours, filtered to obtain the crude valsartan product, and directly put into the valsartan finished product crystallization process without drying.

[0192] Put the crude valsartan obtained in the previous step into the reaction flask, then add 540 mL of ethyl acetate, be warming up to 40 ~ 45 ℃ and stir until the dissolution is clarified, then slowly cool down to -5 ~ 5 ℃, continue to crystallize for 2 hours, stop stirring , filtered, and then washed with 50 mL of ethyl acetate at 0 to 2° C., and dried to obtain 73.7 g of valsartan finished product with a yield of 86%.

[0193] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. The content of each impurity was calculated by the standard curve method; the detection result N-nitrosodimethylamine (NDMA) content was 22.6ppm, valsartan impurity K content was 47.5ppm, valsartan N-chloride was not Check out.

[0194] Comparative Example 2

[0195] Add 100mL of the N,N-dimethylformamide (DMF) solution of valsartan cyanide intermediate (containing 60g of valsartan cyanide intermediate) to the reaction flask, followed by adding 34g of anhydrous zinc chloride and the sodium azide of 25g, be warming up to 130 ~ 135 ℃ of lower stirring reaction 28 hours, after the reaction finishes, be cooled to 30 ~ 50 ℃, then add 40mL DMF, 2400mL methyl tertiary butyl ether and 150mL water, 30 ~ 50 Stir for 1 hour at ℃, cool to 0-10 ℃, then add 16 g of sodium hypochlorite, stir for 30 min, and slowly add 100 mL of 6mol/L dilute sulfuric acid solution dropwise at 0-10 ℃ under stirring until the pH value of the solution is 1-2, let stand, The organic layer was separated.

[0196] The organic layer separated above was transferred to another reaction flask, cooled to 5-10° C., then 60 mL of 30% NaOH aqueous solution and 100 mL of water were added, and the reaction was stirred for 15 to 20 hours. The temperature was further reduced to 0-10°C, 6mol/L hydrochloric acid solution was added dropwise until the pH value was 1-3, then 550mL of ethyl acetate was added, the water layer was separated after stirring for 30 minutes, and then 50g of anhydrous magnesium sulfate was added and stirred for 2 hours , to a moisture content of 0.21%, filtered to remove magnesium sulfate, then 340 mL of ethyl acetate was evaporated under reduced pressure at 40 ° C, cooled to 0 to 5 ° C, crystallized for 8 hours, filtered to obtain crude valsartan, and directly put into it without drying. Crystallization process of valsartan finished product.

[0197] The valsartan crude product obtained in the previous step was put into the reaction flask, then 300 mL of ethyl acetate was added, the temperature was raised to 40 ~ 42°C and stirred until the dissolution was clarified, then slowly cooled to 0 ~ 5°C, continued crystallization for 2 hours, stopped stirring, Filtration, followed by washing with 30 mL of ethyl acetate at 0-2° C., and drying to obtain 56.6 g of finished valsartan, with a yield of 88%.

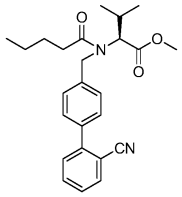
[0198] N-nitrosodimethylamine (NDMA) in valsartan finished product was detected by GC-MS method, and valsartan impurity K and valsartan N-chloride in valsartan finished product were detected by LC-MS method. The content of each impurity was calculated by standard curve method; the detection result was that N-nitrosodimethylamine (NDMA) and impurity K of valsartan were not detected, and the content of valsartan N-chloride was 28.3ppm.

[0199] The above only describes the preferred embodiments of the present invention in detail, and the present invention is not limited to the above-mentioned embodiments, and any transformation and modification of the present invention belong to the protection scope of the present invention.

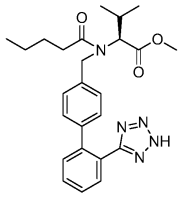
claims

[Claim 1] A method for synthesizing valsartan, characterized in that the prepared valsartan does not contain N-nitrosodimethylamine, valsartan impurity K and valsartan N-chloride; the method comprises the following Steps: (1) Synthesize the valsartan methyl ester intermediate to obtain a reaction mixture containing the valsartan methyl ester intermediate; Preferably, the step (1) comprises: synthesizing the valsartan cyanide intermediate Dissolved in N,N-dimethylformamide, then adding azide and the first acid, heating and stirring to carry out tetrazolium ring-forming reaction, synthesizing the valsartan methyl ester intermediate, thereby obtaining a valsartan methyl compound containing The reaction mixture of the ester compound intermediate; (2) the reaction mixture is diluted with brine or water, and the first extraction solvent is added, and the valsartan methyl ester compound intermediate is extracted by heating; The first organic layer containing the valsartan methyl ester intermediate is obtained; the first organic layer is washed at least once with brine or water, and the aqueous layer is separated to obtain the second organic layer containing the valsartan methyl ester intermediate; preferably Ground, the separated water layers of step (2) are combined, and the azide in the separated water layer is quenched with a quenching agent under acidic conditions; (3) to the middle containing valsartan methyl ester compound Add alkaline solution to the second organic layer of the body, stir for hydrolysis, stand for stratification, after separating the organic layer, adjust the pH of the aqueous layer to acidity with the second acid, and then add the second extraction solvent to the aqueous layer to extract Valsartan compound; stand for stratification to obtain the third organic layer containing the valsartan compound; control the moisture content in the third organic layer to be lower than the target value by adding a desiccant or dewatering by distillation; when the third organic layer is The solvent in the layer is partially concentrated, or the solvent in the third organic layer is evaporated to dryness, and after adding a new solvent, crystallization and filtration can obtain the crude valsartan; Preferably, the target value is 2% by mass, It is preferably 1%, more preferably 0.5%, and most preferably 0.35%; (4) the crude valsartan is added to the crystallization solvent, heated to dissolve, cooled and then incubated for crystallization,

filtered, and the filter cake is washed with the crystallization solvent, Dry to obtain valsartan finished product; Described valsartan cyanide intermediate and valsartan methyl ester intermediate structure are respectively following formula I and formula II:

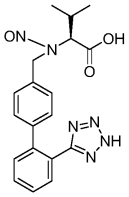


式 I

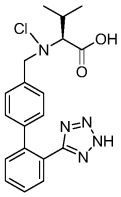


式 II。

[Claim 2] method according to claim 1, is characterized in that, described valsartan impurity K, its structural formula is as follows:



缬沙坦杂质K；described valsartan N-chloride, its structural formula is as follows:



缬沙坦N-氯代物 。

[Claim 3] The method according to claim 1 or 2, wherein the azide described in step (1) is selected from sodium azide, potassium azide, lithium azide, cesium azide and trimethyl azide One or any combination of base silicon azide; preferably, the azide is selected from sodium azide, potassium azide or trimethyl silicon azide.

[Claim 4] The method according to any one of claims 1-3, wherein the first acid described in step (1) is Lewis acid; preferably, the first acid is selected from triethylamine hydrohalic acid Salt, triethylamine sulfate, triethylamine hydrogen sulfate, triethylamine phosphate, triethylamine hydrogen phosphate, trimethylamine hydrogen halide, trimethylamine sulfate, trimethylamine hydrogen sulfate, trimethylamine phosphate , trimethylamine hydrogen phosphate, diisopropylethylamine hydrogen halide, diisopropylethylamine sulfate, diisopropylethylamine hydrogen sulfate, diisopropylethylamine phosphate, pyridine hydrohalic acid salt, pyridine sulfate, pyridine hydrogen sulfate, pyridine phosphate, pyridine hydrogen phosphate, N-methyl morpholine hydrogen halide, N-methyl morpholine sulfate, N-methyl morpholine hydrogen sulfate, N-Methylmorpholine Phosphate, N-Methylmorpholine Hydrogen Phosphate, N-Methylpiperidine Hydrohalide, N-Methylpiperidine Sulfate, N-Methylpiperidine Hydrogen Sulfate, N -Methylpiperidine Phosphate, N-Methylpiperidine Hydrogen Phosphate, N-Methyl Tetrahydropyrrole Hydrohalide, N-Methyl Tetrahydropyrrole Sulfate, N-Methyl Tetrahydropyrrole Hydrogen Sulfate , one of N-methyltetrahydropyrrole phosphate, N-methyltetrahydropyrrole hydrogenphosphate, tributyltin chloride, anhydrous zinc chloride, zinc chloride dihydrate, anhydrous titanium tetrachloride or any combination thereof; More preferably, the first acid described in step (1) is selected from triethylamine hydrogen chloride, triethylamine sulfate, triethylamine hydrogen sulfate, pyridine hydrochloride or anhydrous chlorine Zinc.

[Claim 5] The method according to any one of claims 1-4, wherein the temperature range of the tetrazolium cyclization reaction in step (1) is 70-180°C; the preferred reaction temperature range is 100-140°C .

[权利要求6] 根据权利要求1-5中任一项所述的方法，其特征在于，步骤(2)中所 述的盐水选自氯化钠水溶液、氯化镁水溶液、氯化钾水溶液、氯化钙水溶液、硫酸钠水溶液中的一种或其任意组合； 优选地，步骤(2)中所述的盐水为饱和氯化钠水溶液或质量分数为10～20%的氯化钠水溶液。

[权利要求7] 根据权利要求1-6中任一项所述的方法，其特征在于，步骤(2)中所述的第一提取溶剂为可以溶解缬沙坦甲酯化物中间体，并与水不互溶的有机溶剂； 优选地，步骤(2)中所述的第一提取溶剂选自甲苯、二甲苯、二氯甲烷、甲基叔丁基醚、异丙醚、正丁基醚、苯甲醚、苯乙醚、正己醚、正庚醚中的一种或其任意组合；更优选地，第一提取溶剂选自甲苯、二甲苯、甲基叔丁基醚、苯甲醚或正丁基醚。

[权利要求8] 根据权利要求1-7中任一项所述的方法，其特征在于，步骤(2)中加热提取时的加热温度范围为35-140°C，优选温度范围为45-100°C。

[权利要求9] 根据权利要求1-8中任一项所述的方法，其特征在于，所述的淬灭剂选自亚硝酸盐、次氯酸盐或次溴酸盐中的一种或其任意组合，优选地选自亚硝酸钠、亚硝酸钾、次氯酸钠、次溴酸钠、次溴酸钙、次氯酸钙中的一种或其任意组合，更优选地选自亚硝酸钠或次氯酸钠。

[权利要求10] 根据权利要求1-9中任一项所述的方法，其特征在于，对水层中的叠氮化物淬灭时，形成酸性条件所用的酸为无机强酸，优选为盐酸、硫酸中的一种或其组合；加酸后调节pH值范围为0-5，优选为1-3。

[权利要求11] 根据权利要求1-10中任一项所述的方法，其特征在于，步骤(3)中所述的碱溶液为氢氧化物水溶液、碳酸盐水溶液中的一种或其组合，优选为质量分数30%的氢氧化钠水溶液或质量分数30%的氢氧化钾水溶液。

[权利要求12] 根据权利要求1-11中任一项所述的方法，其特征在于，步骤(3)中加入碱溶液后搅拌进行水解反应，水解反应温度范围为-10-40°C，优选为0-20°C； 优选地，水解反应时间范围为5-40小时，优选为15-25小时。

[权利要求14] 根据权利要求1-13中任一项所述的方法，其特征在于，步骤(3)中所述的将水层用第二酸调节pH至酸性的步骤，所用的第二酸为无机强酸，优选为盐酸、硫酸中的一种或其组合；加酸后调节pH值的范围为0.5-6，优选为1-3。

[权利要求15] 根据权利要求1-14中任一项所述的方法，其特征在于，步骤(3)中所用的第二提取溶剂为可以和水层分层的溶剂，优选为乙酸乙酯或甲基叔丁基醚。

[权利要求16] 根据权利要求1-15中任一项所述的方法，其特征在于，步骤(3)中所述新溶剂为可以溶解缬沙坦的单一溶剂或多个溶剂的混合物； 优选地，所述新溶剂选自乙酸乙酯、丙酮、乙醇、异丙醇或乙酸乙酯与二氯甲烷的混合溶剂； 更优选地，在所述乙酸乙酯与二氯甲烷的混合溶剂中，乙酸乙酯与二氯甲烷体积比为1:3～3:1。

[权利要求17] 根据权利要求1-16中任一项所述的方法，其特征在于，步骤(3)中所述的干燥剂选自无水氯代物金属盐、无水硫酸金属盐中的一种或其组合，优选地选自无水硫酸镁或无水硫酸钠。

[权利要求17] The method according to any one of claims 1-16, wherein the crystallization solvent described in the step (4) is a single solvent that can dissolve valsartan and a mixture of multiple solvents, preferably ethyl acetate Or a mixed solvent of ethyl acetate and dichloromethane; more preferably, in the mixed solvent of ethyl acetate and dichloromethane, the volume ratio of ethyl acetate to dichloromethane is 1:3 to 3:1.